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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/991,628	STOMINGER ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 8/31/05 is acknowledged, and has been entered.

Claims 32-42 are pending and are presently being acted upon.

The following are new grounds of rejection necessitated by Applicant's amendment filed 8/31/05.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 32-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed inventions.

The instant claims encompass: (1) a pharmaceutical preparation for tolerization comprising a pharmaceutically acceptable carrier and (a) an "isolated human polypeptide" or (b) an "isolated human pathogen polypeptide" effective for tolerizing an individual to an autoantigen, said human polypeptide consisting of a sequence motif for an HLA-DR protein containing the core MHC binding residues, wherein said HLA-DR protein is selected from the group consisting of HLA-DR2 and HLA-DR4 associated with one of the human autoimmune diseases PV or MS, wherein the polypeptide binds the said HLA-DR protein and activates autoreactive T cells from a subject having the said autoimmune disease and wherein the polypeptide is a non-MBP polypeptide, or (2) a method of tolerizing an individual to an autoantigen of PV comprising administering an effective amount of the pharmaceutical preparation of "(1)(a)" above to a subject in need of such treatment.

Furthermore, the instant claims encompass a pharmaceutical composition for tolerizing an individual to an autoantigen, said composition comprising a polypeptide that binds to an HLA-DR2 or HLA-DR4 allele and activates autoreactive T cells from a subject having PV or MS, wherein:

- the said HLA-DR2 or HLA-DR4 allele is associated with PV or MS and wherein the polypeptide does not have to be a subsequence of a protein found in human-infecting pathogens (*i.e.,* the recitation of "human pathogen polypeptide" in base claim 41; what amino acid residues confer "human pathogen" character upon an amino acid sequence), and wherein the polypeptide may possess partial structure in having some or all anchor residues for binding to some said HLA-DR2 or HLA-DR4 allele (claims 41 and 42)
- the said HLA-DR2 or HLA-DR4 allele is associated with PV or MS and wherein the polypeptide does not have to be a subsequence of an autoantigen associated with PV or MS or of any protein, and wherein the polypeptide may possess partial structure in having some or all anchor residues for binding to some said HLA-DR2 or HLA-DR4 allele (claims 32-34, 37 and 38)
- the said HLA-DR2 or HLA-DR4 allele is associated with PV or MS and wherein the composition comprises a polypeptide of undisclosed partial structure that comprises the PV#1 motif (SEQ ID NO: 21) for P1, P4 and P6 anchor residues for peptide binding to HLA-DRβ1*0402, and said polypeptide does not have to be a subsequence of any protein or of desmoglein-3 or of an undisclosed autoantigen protein (claim 34)
- or the composition *useful for tolerization* that comprises a polypeptide that consists of one of SEQ ID NO: 1-7 or a subsequence of one of SEQ ID NO: 1-7 (*i.e.,* the recitation of "***an*** amino acid sequence of" in claim 35, emphasis by Examiner) (claim 35)
- or the composition *useful for tolerization* that comprises a polypeptide of undisclosed partial structure that comprises one of SEQ ID NO: 18-20, which are MS #1-3 motifs for binding to HLA-DR2 allele HLA-DRβ1*1501 (with P1 and P4 anchor residues and P-1, P2, P3 and P5 TCR contact residues) (claim 39);

and wherein the human polypeptide is a non-myelin basic protein polypeptide.

The instant claims also encompass a method of tolerizing a patient to an autoantigen of PV comprising administering a pharmaceutical composition:

- that comprises a polypeptide as in "(1)(a)" above that is not necessarily a subsequence from the PV-associated autoantigen desmoglein-3, is not a subsequence from an autoantigen, is not a subsequence from any protein, and has a sequence motif for binding to an HLA-DR2 or HLA-DR4 molecule that is associated with PV (claim 36),
- that consists of one of SEQ ID NO: 1-7 or a subsequence of one of SEQ ID NO: 1-7 (*i.e.,* the recitation of "***an*** amino acid sequence of" in claim 35, emphasis by Examiner) (claim 36), or a polypeptide of undisclosed partial structure that comprises the PV#1 motif for P1, P4 and P6 anchor residues (claim 36)
- that comprises a polypeptide of undisclosed partial structure that comprises the PV#1 motif (SEQ ID NO: 21) for P1, P4 and P6 anchor residues for peptide binding to HLA-DRβ1*0402, and which does not have to be a subsequence of any protein or which may be a subsequence of an undisclosed autoantigen protein (claim 36)

The specification does not provide adequate written description for a pharmaceutical preparation for tolerization comprising an "isolated human polypeptide" or "an "isolated human pathogen polypeptide"...consisting of a sequence motif for an HLA-DR4 or HLA-DR2 protein containing the core MHC binding residues" that "activates autoreactive T cells from a subject having PV or MS" nor does it provide adequate written description of what those MHC core binding residues are, nor of the structure of HLA-DR2 or HLA-DR4 protein peptide binding site and associated sequence motifs, nor of a method for tolerizing an individual to an autoantigen of PV comprising administering the preparation of "(1)(a)" above.

The specification does not disclose what amino acid residues are associated with a *human* polypeptide or a *human* pathogen polypeptide, *i.e.,* if the polypeptide of the instant claims is not a subsequence of a human protein or a human pathogen protein, what amino acid residues present at non-anchor positions confer "human" or "human pathogen" to the polypeptide. The specification discloses (on page 51 at the last 7 lines) that by "human pathogen" it is meant a bacterium, a virus or a protozoan capable of infecting humans and generating an immune response. The specification does not disclose which amino acid residues are associated with "human pathogen polypeptides" that infect other species as well as humans. There is no disclosure of any "human pathogen polypeptide" that is associated with PV, nor of any "isolated human polypeptide" or protein comprising a subsequence that is an

"isolated human polypeptide" other than those that derive from desmoglein-3 for PV.

The specification on page 52 at lines 25-27 discloses that the term "core MHC binding residues" means the residues of an epitope corresponding to the P-1 to P-9 positions of a peptide bound to an HLA-DR molecule. The specification further discloses that there are 5 binding pockets in MHC (class II, DR), P1, P4, P6, P7 and P9 (page 19 at lines 17-25), at least two of which (page 19 at lines 29-31, page 20, lines 5-6) are used via consideration of the chemical nature and size of said binding pockets (page 20 at lines 9-23) for determination of the sequence motif of the corresponding peptide that binds to the MHC molecule (page 19 at lines 29-31).

The specification discloses (page 15 at lines 20-23) the pocket 1 amino acid residues for HLA-DRβ1*0101, and that the "corresponding residues for other HLA-DR alleles are known in the art (see, *e.g.,* Marsh and Bodmer, 1992, incorporated by reference herein) and are available through genetic databases." The specification does not disclose which HLA-DR alleles are known in the art at the time the invention was made, nor what the structure of the peptide binding site is for each corresponding HLA-DR allele, nor what the sequence motif is, nor what the core binding residues are. The specification further discloses that "...before or after the pockets to be restricted by the motif are selected, the set of amino acid side chains likely to bind within each of those pockets, and therefore, the set of amino acid residues that will define the corresponding positions of the motif, must be determined. This may be accomplished by one of ordinary skill in the art by considering the amino acid residues that form the pocket. These residues, identified in Section A above, will determine the size and nature (*i.e.,* hydrophobic, hydrophilic, positively charged, negatively charged, uncharged) of the pocket and consequently, the side chains which may bind within the pocket." (page 20 at the second paragraph). The specification discloses for one of the identified pockets P6, that the alpha chain amino acid pocket residues are relatively conserved among HLA-DR molecules, but that the two beta chain amino acid residues, β11 and β13 vary widely among the DR alleles (page 17 at the two full paragraphs). The specification further discloses that in DR alleles wherein β13 is occupied by smaller or more polar residues such as the β13 His of DRβ1*0401, the P6 motif may include somewhat larger and polar residues (*e.g.,* S, T, V) but should still avoid the largest and aromatic residues, and in some alleles β11 and β13 are both serine residues (*e.g.,* DRβ1*1101) and for these cases more hydrophilic or hydrogen bonding residues may be included in the motif (page 17 at the second full paragraph).

The specification discloses that HLA-DR4 (DRβ1*0402) or a rare HLA-DQ1 (DQβ1*05032) allele (page 2) are associated with the autoimmune disease pemphigus vulgaris (PV), and that HLA-DRβ1*1501, *i.e.,* HLA-DR2, or DQ1 are associated with MS disease susceptibility (page 2). Other than HLA-DRβ1*0402, no other HLA-DR4 subtypes are disclosed by the specification as being associated with susceptibility to PV, and other than HLA-DRβ1*1501, no other HLA-DR2 subtypes are disclosed by the specification as being associated with susceptibility to MS.

The specification discloses (page 37 at line 8 through page 38) that although the autoantigen for PV is known *(i.e.,* desmoglein 3, 130kDA, 999 amino acid residues in length), the precise epitopes within the autoantigen have remained previously unknown, and that using the method of the present invention (*i.e.,* the PV#1 motif), a set of 7 peptides were identified that matched the motif and that may be potential autoantigenic determinants for T cell dependent induction of PV. The specification further discloses that T cell lines were raised from blood mononuclear cells of two patients with active disease, expanded in rIL-2 and tested for recognition of the candidate peptides, the result being that SEQ ID NO: 3 and 4 (two peptides from the extracellular domain of desmoglein 3 that are located close to the major autoantibody recognition site) were recognized. The specification does not disclose if the other five peptides are capable of binding to HLA-DR4 (DRβ1*0402, DR4Dw10), nor if they can be recognized by atuoreactive T cells from PV patients, nor if they can be used for immunization or tolerization in such patients.

The specification does not disclose working examples of administration of any polypeptide to an individual *in vivo* to tolerize against any autoantigen, nor to achieve any therapeutic endpoint.

Evidentiary reference Rammensee *et al* (MHC Ligands and Peptide Motifs, 1997, pages 200, 204-205 and 227) teaches that for alleles that possess β11 and β13 that are both serine residues, the anchor residues are actually large basic amino acid residues (R, K, H) for DRβ1*1101 and DRβ1*1104, and (R, K) for DRβ1*1301 and DRβ1*1302, in contrast to Applicant's disclosure of the general class of hydrophilic or hydrogen bonding residues which would include acidic amino acid residues. Rammensee *et al* further teaches that the anchor residues for DRβ1*0401 are N, S, T, Q, H, R, the said residues including the "largest and aromatic residues" that Applicant's disclosure predicts should be avoided based upon the structure of the P6 pocket. Rammensee *et al* teach that the P4 anchors for HLA-DRβ1*0402 include Y, F, W, I, L, M, R and N in contrast to Applicant's disclosure that predicts in addition to R, K at P4, but not Y, F, W, I, L, M and N.

Rammensee *et al* further teach that although peptide motifs proved extremely helpful in the identification of MHC class I restricted T cell epitopes, for the description of new class II-restricted epitopes, however, conventional epitope mapping still represents the state of the art. Rammensee *et al* teach this is mainly because of the highly degenerate anchor positions in MHC class II presented peptides. Rammensee *et al* teach combining other strategies that value the role of every amino acid residue, not just anchor residues, in the interaction with the MHC class II binding cleft (especially page 227 at Prediction of MHC II Restricted Epitopes section).

Evidentiary reference Reche *et al* (Immunogenetics 2004, 56: 405-419) teach that although anticipation of T cell epitopes is heavily predicated on the prediction of peptide MHC binding, yet prior to MHC binding, correct peptide processing must occur to liberate a peptide from its protein source (first sentence of first full paragraph at column 1 on page 406), and the complexity of such processing makes identification of any pattern related with processing of class II restricted peptides difficult. Reche *et al* teach that cleavage site prediction methods are important adjuncts for T-cell epitope discovery (abstract). Reche *et al* teach that conserved regions flanking the core CD4 T cell epitopes (*i.e.,* class II binding epitopes) may contribute to immunogenicity, said regions being related to antigen processing rather than peptide/MHC interaction (last paragraph of article).

Evidentiary reference O'Sullivan (Applicant's IDS reference) teaches that the presence of putative binding motif residues does not necessarily correlate with actual binding to an MHC molecule because both binders and non-binders may have the putative motif.

The specification discloses that the peptide may be administered in high doses to produce high dose tolerance (page 30 at lines 15-18), *i.e.,* that peptides that are immunogenic can be used at high doses to induce tolerance.

The art recognizes that in order to be used for generating an immunogenic or tolerogenic response that said peptide must bind MHC and also present an epitope recognized by T cells. The art recognizes that the T cell epitope differs from the amino acids pertinent to MHC binding.

Evidentiary reference Karin *et al* (J. Exp. Med. 1994, 180: 2227-2237, of record) teaches that a single substitution in an amino acid residue, wherein said amino acid residue plays no role in MHC binding, can completely abrogate the immunogenicity of an otherwise immunogenic peptide (especially summary and Table 1). Thus Karen *et al* establish that amino acid residues not recited in the claimed "human" or "human pathogen" polypeptides, *i.e.,* TCR contact residues, will play a pivotal role in determining whether the peptides recited in the claims are capable of being immunogenic, and by extension tolerogenic.

Evidentiary reference Tisch and McDevitt (PNAS USA 1994, 91: 437-438, of record) teach that the high degree of specificity required for the process of clonal deletion/anergy may be limiting when dealing with diseases such as MS in which there are responses to several autoantigens and the critical inciting autoantigen(s) is not known (page 437, column 3 at the third full paragraph). Tisch and McDevitt teach that only in EAE, where defined antigens (MBP or Ac1-11 MBP peptide) have been used to induce disease, has antigen-specific immunotherapy clearly succeeded in treating an ongoing autoimmune response, and that the critical tests of systemic antigen-specific immunotherapy have yet to be done (page 438, column 1 at lines 6-12).

Evidentiary reference Schwartz and Kipnis (The Neuroscientist 2002, 8(5): 405-413) teach that immunosuppression as a therapeutic strategy for CNS dysfunction should be weighed with extreme caution (last sentence of article). Schwartz and Kipnis teach that in patients with MS and other neurodegenerative diseases, where the aim is to block the autoimmune disorder while deriving the potential benefit of the autoimmune response, the effect of treatment should be immunomodulatory rather than immunosuppressive (abstract and the paragraph spanning pages 411 and 412).

There is no written description in the specification of the amino acids that constitute the T cell epitope in the peptide recited in the claim. With the exception of the specific peptides identified by amino acid sequence in the specification such as SEQ ID NO: 1-7 from the contiguous sequence of the PV autoantigen protein desmoglein 3, or such as SEQ ID NO: 8-15 from pathogen associated proteins, the skilled artisan cannot envision the detailed structure of the encompassed peptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. In the instant application, the amino acid itself or isolated peptide is required.

See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1404-7 (Fed. Cir. 1997). In University of California v. Eli Lilly and Co., 39 U.S.P.Q.2d 1225 (Fed. Cir. 1995) the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The court held that only the nucleic acids species described in the specification (i.e. nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, id. at 1240. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials. . .conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 016 (Fed. Cir. 1991). Attention is also directed to the decision of The Regents of the University of California v. Eli Lilly and Company (CAFC, July 1997) wherein is stated: "The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA." See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606.

Applicant's arguments in the amendment filed 8/31/05 have been fully considered but are not persuasive.

Applicant's position in the said amendment beginning on pages 4-13 under the section entitled "Claim rejections under 35 U.S.C. 112, first paragraph-Written Description" is of record. Briefly, this is: (1) that the claimed genus of human polypeptides or human pathogen polypeptides are defined by both structural and functional terms, similar to various polynucleotides in Example 9 of the "Revised Interim Written Description Guidelines Training Materials", with the sequence motif providing the structural description recited in the instant claims, *i.e.,* "core MHC binding residues", as well as the disclosure in the specification of the general approach to derive sequence motifs for any disease-associated HLA allele by describing the pocket structures for each of the key MHC contact residues of the sequence motif (P1, P4, P6, P7 and P9) and the general criteria for selecting the TCR contact residues (P-1, P2, P3, P5, P8 and P11), (2) Applicant has described the claimed genus by describing a representative number of species, (3) the HLA-DR proteins must be of the DR2 or DR4 subtype and be associated with MS or PV, (4) that PV is associated with one DR4 allele, DRB1*0402, and a rare DQ1 allele (DQB1*05032), and MS is associated with the most common DR2 subtype, DRB1*1501 and DQ1, and their sequences were well known at the time of filing, (5) two specific examples relating to the PV and MS sequence motifs are described, PV motif#1 and MS motifs #1-3, (6) DRB1*0402 was the only known PV-associated HLA-DR4 allele at the time of filing, and DRB1*1501 was the only known MS-associated HLA-DR2 allele at the time of filing, and their sequences and binding pocket structures are described and motifs are described for peptides that bind to each, therefore, any later identified PV- or MS-associated HLA alleles, if any at all, may yield similar sequence motifs within the scope of the claims, (7) the sequence motifs may be used to search other human proteins or human pathogen polypeptides, and such search is expected to yield additional structurally and functionally similar polypeptides within the claimed genus, *i.e.,* they have the structural limitation of possessing a binding motif and the functional limitations of binding HLA-DR and stimulating autoreactive T cells, (8) that the Ramensee et al reference does not contradict the disclosure of the instant specification, (9) that different polypeptides are expected to bind to different TCR, thus involving different T cell contact residues.

It is the Examiner's position that the instant claims are drawn to a pharmaceutical composition for tolerization and method for tolerizing an individual to an autoantigen of PV or MS, that the "human" or "human pathogen" polypeptides comprised in the said composition or used in the claimed method must be capable of binding to an HLA-DR2 or HLA-DR4 protein *and* be capable of tolerizing an individual to an autoantigen of PV or MS. It is the Examiner's further position that the claimed genus of "human" polypeptides or "human pathogen" polypeptides are not defined by both structural and functional terms.

Although Applicant has described the five binding pockets in MHC class II DR molecules, what position corresponding amino acid residues side-chains must be at of peptides that bind to said molecules, and what position the TCR contact residues are at in the said polypeptides, the specification does not disclose what the TCR contact residues are, nor if the polypeptides are subsequences of proteins, *i.e.,* what amino acid sequences make a polypeptide "human" or "human pathogen", nor if they *are* subsequences of proteins, which "human" or "human pathogen" proteins out of millions of potential proteins found exclusively in humans or in pathogens that infect humans are those which contain subsequences that bind to particular HLA-DR2 and HLA-DR4 alleles associated with PV or MS *and* can tolerize against an autoantigen of PV or MS.

No structure-function correlation is disclosed by the instant specification to describe which HLA binding peptides contain TCR contact residues that render the peptide an epitope, *i.e.,* immunogenic, or by extension, "tolerogenic".

It is the Examiner's position that even if polypeptides comprise one of the SEQ ID NO: 18-20 motifs that comprise both two anchor residues and three to four TCR contact residues, there is no guarantee that a peptide designed on the basis of one of the said motifs would be immunogenic or tolerogenic for an autoantigen, whether it is a subsequence of a protein or not.

It is the Examiner's further position that although the instant specification discloses that one DR4 allele DRB1*0402 is associated with PV and the most common DR2 subtype DRB1*1501 is associated with MS, the specification does not disclose which proteins or amino acid sequences are associated with activation of an MBP or desmoglein 3-specific T cell from an MS patient or a PV patient or of any T cell specific for an undisclosed autoantigen of MS or PV, except for peptides consisting of SEQ ID NO: 8-15 and of SEQ ID NO: 3 and 4, respectively, nor which proteins besides desmoglein 3 or those associated with the pathogen associated peptides SEQ ID NO: 8-15 possess subsequences that contain

such epitopes. There is no description of whether these said SEQ ID NO can produce the desired effect of tolerization *in vivo*.

In addition, it is the Examiner's position that evidentiary reference Rammensee *et al* (1997) is cited for it's teaching of the correlation of the HLA-DR P6 pocket polymorphic β11 and β13 residues *vs* the anchor residue corresponding to that position in peptides that bind the particular HLA-DR subtype allele. The said reference teaches that basic amino acid residues (R, K, H) are anchor residues for actual peptides that bind to the HLA-DR subtypes that have β11 Ser and β13 Ser. This teaching is in contrast to Applicant's specification that discloses methods of anchor residue *prediction* based upon the pocket amino acid residues in the particular class II MHC molecule, Applicant's said method predicts a P6 anchor residue that can be basic *or* acidic (both are "hydrophilic"), *i.e.,* Applicant's disclosure is to the general class of hydrophilic or hydrogen bonding residues, which is not what is found when the anchor residues are actually defined experimentally. Further, Rammensee *et al* teach that the anchor residues for DR β1*0401 are N, S, T, Q, H, and R based upon actual discovery, yet Applicant's predictive method discloses that somewhat larger residues such as S, T and V may be present at P6, but that largest and aromatic residues should be avoided. N, Q, H and R are large amino acid residues, yet they are P6 anchor residues in peptides that bind DR β1*0401, contrary to Applicant's disclosure as to S, T and V as DR β1*0401 P6 anchor residues. Rammensee *et al* teach that the P4 anchors for the PV-associated HLA-DRβ1*0402 allele include Y, F, W, I, L, M, R and N, in contrast to Applicant's disclosure that *predicts* in addition to R, that K will be present at P4, and does not predict Y, F, W, I, L, M and N which are actual anchor residues. In addition, in response to Applicant's assertion that the specification discloses the only known HLA-DR4 allele associated with PV, the specification discloses that a small fraction of PV patients do not have the HLA-DR4 or DQ1 susceptibility genes.

It is the Examiner's position that a definition by function in the absence of sufficient structural information does not provide adequate written description for the reasons enunciated in this rejection. A definition by function does not suffice to define the genus because it is only an indication of what the property the peptide has, and if one extends the analysis in the instant case, what the peptide does (*i.e.,* it binds to an HLA-DR2 or an HLA-DR4 molecule and activates autoreactive T cells from a subject having PV or MS, and so can be used to tolerize against an autoantigen), rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many such species may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if

one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

It is the Examiner's further position that SEQ ID NO: 1 of the cited Example 9 of the Written Description Guideline's Training Materials is a fully defined sequence (with functional property of binding a specific receptor to stimulate a specific activity) that would yield structurally similar DNAs under stringent hybridization conditions, whereas the instant case is of a polypeptide that may or may not be a subsequence of some undisclosed protein that may or may not be an autoantigen of PV or MS or that may or may not be a subsequence of a protein from one of any undisclosed pathogens, that may be derived from a partial binding motif that is in turn derived in many cases from predictions made from HLA-DR2 or HLA-DR4 allele pocket amino acid residues, that may not in fact stimulate a T cell, and in addition, where the polypeptide is not a subsequence of a protein, the TCR contact amino acid residues may be any of a large number of possible amino acid residues. In the said Example 9, fully defined sequences would be derived from the said hybridization, in contrast to the instant case, and so one of ordinary skill in the art would expect substantial variation among species. It is the Examiner's position that the claims are not limited to a polypeptide that is a subsequence of desmoglein-3. It is the Examiner's position that the number of potential polypeptides is very large due to the number of proteins (Applicant estimates this as no more than 100 proteins/viral genome) in an undisclosed number of pathogens, *i.e.,* for example, 100 proteins x 100 pathogens = 100,000 proteins, and 100,000 proteins contain an undisclosed number of subsequences possessing a motif for binding to a subtype of HLA-DR2 or HLA-DR4 associated with PV or MS. If just 10 peptide subsequences exist per protein, that is 1 million peptides. Applicant estimates less than 50,000 human proteins exist. This would constitute several million subsequences that would potentially possess the binding motif. If the polypeptides possessing the motif are not subsequences of proteins, then the number of potential polypeptides that could possess the motif is potentially unlimited, as the TCR contact amino acid residues are not specified. In addition, evidentiary reference Reche *et al* teach that conserved regions flanking the core CD4 T cell epitopes (*i.e.,* class II binding epitopes) may contribute to immunogenicity, adding to the number of potential peptides.

With regard to Applicant's argument as to a subsequent article published by the inventors (Wucherpfennig *et al.* PNAS USA 12/1995, 92: 22935-22939) teaching that SEQ ID NO: 5 and 7 react with autoreactive T cells from other PV patients different from the autoreactive T cells that react with SEQ ID NO: 3 and 4, it is the Examiner's position that this teaching is illustrative of other factors that govern immunogenicity of peptides, *i.e.,* T cell repertoire in various individuals, immunodominance of particular epitopes, and possibly epitope spreading over the course of a disease, to name a few.

4. Claims 32-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 32-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical preparation comprising a human polypeptide consisting of one of SEQ ID NOS: 3 and 4, does not reasonably provide enablement for the claimed pharmaceutical preparation comprising one of SEQ ID NO: 1, 2, 5, 6 or 7, nor an "isolated human polypeptide" or an "isolated human pathogen polypeptide" consisting of an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR2 or an HLA-DR4 protein associated with PV and wherein the said polypeptide activates autoreactive T cells from a subject having PV or MS, nor a method of tolerizing an individual to an autoantigen of PV comprising administering the said pharmaceutical composition comprising the polypeptide wherein the polypeptide is not one of SEQ ID NO: 3 or SEQ ID NO: 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass: (1) a pharmaceutical preparation for tolerization comprising a pharmaceutically acceptable carrier and (a) an "isolated human polypeptide" or (b) an "isolated human pathogen polypeptide" effective for tolerizing an individual to an autoantigen, said human polypeptide consisting of a sequence motif for an HLA-DR protein containing the core MHC binding residues, wherein said HLA-DR protein is selected from the group consisting of HLA-DR2 and HLA-DR4 associated with one of the human autoimmune diseases PV or MS, wherein the polypeptide binds the said HLA-DR protein and activates autoreactive T cells from a subject having the said autoimmune disease and wherein the polypeptide is a non-MBP polypeptide, or (2) a method of tolerizing an individual to an autoantigen of PV comprising administering an effective amount of the

pharmaceutical preparation of "(1)(a)" above or comprising administering a pharmaceutical preparation comprising one of SEQ ID NO: 1, 2, 5, 6, or 7, said SEQ ID NO may or may not bind an HLA-DR4 or an HLA-DR2 allele and be capable of stimulating an immune response or inducing tolerance, to a subject in need of such treatment. The instant claims encompass a pharmaceutical composition comprising a polypeptide that binds to an HLA-DR2 or HLA-DR4 allele and activates autoreactive T cells from a subject having PV or MS, wherein the said HLA-DR2 or HLA-DR4 allele is associated with PV or MS and wherein the polypeptide does not have to be a subsequence of an autoantigen associated with PV or MS, nor a subsequence of some undisclosed polypeptide of undisclosed structure that is exclusively found in humans or in human pathogens or a method of tolerizing a patient to an autoantigen of PV comprising administering a pharmaceutical composition that comprises a polypeptide that is not necessarily a subsequence from the PV-associated autoantigen desmoglein-3.

Furthermore, the instant claims encompass a pharmaceutical composition for tolerizing an individual to an autoantigen, said composition comprising a polypeptide that binds to an HLA-DR2 or HLA-DR4 allele and activates autoreactive T cells from a subject having PV or MS, wherein:

- the said HLA-DR2 or HLA-DR4 allele is associated with PV or MS and wherein the polypeptide does not have to be a subsequence of a protein found in human-infecting pathogens (*i.e.,* the recitation of "human pathogen polypeptide" in base claim 41; what amino acid residues confer "human pathogen" character upon an amino acid sequence), and wherein the polypeptide may possess partial structure in having some or all anchor residues for binding to some said HLA-DR2 or HLA-DR4 allele (claims 41 and 42)
- the said HLA-DR2 or HLA-DR4 allele is associated with PV or MS and wherein the polypeptide does not have to be a subsequence of an autoantigen associated with PV or MS, and wherein the polypeptide may possess partial structure in having some or all anchor residues for binding to some said HLA-DR2 or HLA-DR4 allele(claims 32-34, 37 and 38)
- the said HLA-DR2 or HLA-DR4 allele is associated with PV or MS and wherein the composition comprises a polypeptide of undisclosed partial structure that comprises the PV#1 motif (SEQ ID NO: 21) for P1, P4 and P6 anchor residues for peptide binding to HLA-DRβ1*0402, and said polypeptide does not have to be a subsequence of any protein or of desmoglein-3 or of an undisclosed autoantigen protein (claim 34)
- or the composition *useful for tolerization* that comprises a polypeptide that consists of one of SEQ ID NO: 1-7 or a subsequence of one of SEQ ID NO: 1-7 (*i.e.,* the recitation of "***an***

amino acid sequence of" in claim 35, emphasis by Examiner) (claim 35)

- or the composition *useful for tolerization* that comprises a polypeptide of undisclosed partial structure that comprises one of SEQ ID NO: 18-20, which are MS #1-3 motifs for binding to HLA-DR2 allele HLA-DRβ1*1501 (with P1 and P4 anchor residues and P-1, P2, P3 and P5 TCR contact residues) (claim 39).

The instant claims also encompass a method of tolerizing a patient to an autoantigen of PV comprising administering a pharmaceutical composition:

- that comprises a polypeptide as in "(1)(a)" above that is not necessarily a subsequence from the PV-associated autoantigen desmoglein-3, is not a subsequence from an autoantigen, is not a subsequence from any protein, and has a sequence motif for binding to an HLA-DR2 or HLA-DR4 molecule that is associated with PV (claim 36),
- that consists of one of SEQ ID NO: 1-7 or a subsequence of one of SEQ ID NO: 1-7 (*i.e.,* the recitation of "***an*** amino acid sequence of" in claim 35, emphasis by Examiner) (claim 36), or a polypeptide of undisclosed partial structure that comprises the PV#1 motif for P1, P4 and P6 anchor residues (claim 36)
- that comprises a polypeptide of undisclosed partial structure that comprises the PV#1 motif (SEQ ID NO: 21) for P1, P4 and P6 anchor residues for peptide binding to HLA-DRβ1*0402, and which does not have to be a subsequence of any protein or which may be a subsequence of an undisclosed autoantigen protein (claim 36)

The specification does not provide adequate disclosure for a pharmaceutical preparation for tolerization comprising an "isolated human polypeptide" or "an "isolated human pathogen polypeptide"...consisting of a sequence motif for an HLA-DR4 or HLA-DR2 protein containing the core MHC binding residues" that "activates autoreactive T cells from a subject having PV or MS" nor does it provide adequate disclosure of what those MHC core binding residues are, nor of the structure of HLA-DR2 or HLA-DR4 protein peptide binding site and associated sequence motifs, nor of a method for tolerizing an individual to an autoantigen of PV comprising administering the preparation of "(1)(a)" above.

The specification does not disclose what amino acid residues are associated with a *human* polypeptide or a *human* pathogen polypeptide, *i.e.,* if the polypeptide of the instant claims is not a subsequence of a human protein or a human pathogen protein, what amino acid residues present at non-anchor positions confer "human" or "human pathogen" to the polypeptide. The specification discloses (on page 51 at the last 7 lines) that by "human pathogen" it is meant a bacterium, a virus or a protozoan capable of infecting humans and generating an immune response. The specification does not disclose which amino acid residues are associated with "human pathogen polypeptides" that infect other species as well as humans. There is no disclosure of any "human pathogen polypeptide" that is associated with PV, nor of any "isolated human polypeptide" or protein comprising a subsequence that is an" isolated human polypeptide" other than those that derive from desmoglein-3 for PV.

The specification on page 52 at lines 25-27 discloses that the term "core MHC binding residues" means the residues of an epitope corresponding to the P-1 to P-9 positions of a peptide bound to an HLA-DR molecule. The specification further discloses that there are 5 binding pockets in MHC (class II, DR), P1, P4, P6, P7 and P9 (page 19 at lines 17-25), at least two of which (page 19 at lines 29-31, page 20, lines 5-6) are used via consideration of the chemical nature and size of said binding pockets (page 20 at lines 9-23) for determination of the sequence motif of the corresponding peptide that binds to the MHC molecule (page 19 at lines 29-31).

The specification discloses (page 15 at lines 20-23) the pocket 1 amino acid residues for HLA-DRβ1*0101, and that the "corresponding residues for other HLA-DR alleles are known in the art (see, *e.g.,* Marsh and Bodmer, 1992, incorporated by reference herein) and are available through genetic databases." The specification does not disclose which HLA-DR alleles are known in the art at the time the invention was made, nor what the structure of the peptide binding site is for each corresponding HLA-DR allele, nor what the sequence motif is, nor what the core binding residues are. The specification further discloses that "...before or after the pockets to be restricted by the motif are selected, the set of amino acid side chains likely to bind within each of those pockets, and therefore, the set of amino acid residues that will define the corresponding positions of the motif, must be determined. This may be accomplished by one of ordinary skill in the art by considering the amino acid residues that form the pocket. These residues, identified in Section A above, will determine the size and nature (*i.e.,* hydrophobic, hydrophilic, positively charged, negatively charged, uncharged) of the pocket and consequently, the side chains which may bind within the pocket." (page 20 at the second

paragraph). The specification discloses for one of the identified pockets P6, that the alpha chain amino acid pocket residues are relatively conserved among HLA-DR molecules, but that the two beta chain amino acid residues, β11 and β13 vary widely among the DR alleles (page 17 at the two full paragraphs). The specification further discloses that in DR alleles wherein β13 is occupied by smaller or more polar residues such as the β13 His of DRβ1*0401, the P6 motif may include somewhat larger and polar residues (*e.g.,* S, T, V) but should still avoid the largest and aromatic residues, and in some alleles β11 and β13 are both serine residues (*e.g.,* DRβ1*1101) and for these cases more hydrophilic or hydrogen bonding residues may be included in the motif (page 17 at the second full paragraph).

The specification discloses that HLA-DR4 (DRβ1*0402) or a rare HLA-DQ1 (DQβ1*05032) allele (page 2) are associated with the autoimmune disease pemphigus vulgaris (PV), and that HLA-DRβ1*1501, *i.e.,* HLA-DR2, or DQ1 are associated with MS disease susceptibility (page 2). Other than HLA-DRβ1*0402, no other HLA-DR4 subtypes are disclosed by the specification as being associated with susceptibility to PV, and other than HLA-DRβ1*1501, no other HLA-DR2 subtypes are disclosed by the specification as being associated with susceptibility to MS.

The specification discloses (page 37 at line 8 through page 38) that although the autoantigen for PV is known *(i.e.,* desmoglein 3, 130kDA, 999 amino acid residues in length), the precise epitopes within the autoantigen have remained previously unknown, and that using the method of the present invention (*i.e.,* the PV#1 motif), a set of 7 peptides were identified that matched the motif and that may be potential autoantigenic determinants for T cell dependent induction of PV. The specification further discloses that T cell lines were raised from blood mononuclear cells of two patients with active disease, expanded in rIL-2 and tested for recognition of the candidate peptides, the result being that SEQ ID NO: 3 and 4 (two peptides from the extracellular domain of desmoglein 3 that are located close to the major autoantibody recognition site) were recognized. The specification does not disclose if the other five peptides are capable of binding to HLA-DR4 (DRβ1*0402, DR4Dw10), nor if they can be recognized by atuoreactive T cells from PV patients, nor if they can be used for immunization or tolerization in such patients.

The specification does not disclose working examples of administration of any polypeptide to an individual *in vivo* to tolerize against any autoantigen, nor to achieve any therapeutic endpoint.

Evidentiary reference Rammensee *et al* (MHC Ligands and Peptide Motifs, 1997, pages 200, 204-205 and 227) teach that for alleles that possess β11 and β13 that are both serine residues, the anchor residues are actually large basic amino acid residues (R, K, H) for DRβ1*1101 and DRβ1*1104, and (R, K) for DRβ1*1301 and DRβ1*1302, in contrast to Applicant's disclosure of the general class of hydrophilic or hydrogen bonding residues which would include acidic amino acid residues. Rammensee *et al* further teaches that the anchor residues for DRβ1*0401 are N, S, T, Q, H, R, the said residues including the "largest and aromatic residues" that Applicant's disclosure predicts should be avoided based upon the structure of the P6 pocket. Rammensee *et al* teach that the P4 anchors for HLA-DRβ1*0402 include Y, F, W, I, L, M, R and N in contrast to Applicant's disclosure that predicts in addition to R, K at P4, but not Y, F, W, I, L, M and N.

Rammensee *et al* further teach that although peptide motifs proved extremely helpful in the identification of MHC class I restricted T cell epitopes, for the description of new class II-restricted epitopes, however, conventional epitope mapping still represents the state of the art. Rammensee *et al* teach this is mainly because of the highly degenerate anchor positions in MHC class II presented peptides. Rammensee *et al* teach combining other strategies that value the role of every amino acid residue, not just anchor residues, in the interaction with the MHC class II binding cleft (especially page 227 at Prediction of MHC II Restricted Epitopes section).

Evidentiary reference Reche *et al* (Immunogenetics. 2004, 56: 405-419) teach that although anticipation of T cell epitopes is heavily predicated on the prediction of peptide MHC binding, yet prior to MHC binding, correct peptide processing must occur to liberate a peptide from its protein source (first sentence of first full paragraph at column 1 on page 406), and the complexity of such processing makes identification of any pattern related with processing of class II restricted peptides difficult. Reche *et al* teach that cleavage site prediction methods are important adjuncts for T-cell epitope discovery (abstract). Reche *et al* teach that conserved regions flanking the core CD4 T cell epitopes (*i.e.,* class II binding epitopes) may contribute to immunogenicity, said regions being related to antigen processing rather than peptide/MHC interaction (last paragraph of article).

Evidentiary reference O'Sullivan (Applicant's IDS reference) teaches that the presence of putative binding motif residues does not necessarily correlate with actual binding to an MHC molecule because both binders and non-binders may have the putative motif.

The specification discloses that the peptide may be administered in high doses to produce high dose tolerance (page 30 at lines 15-18), *i.e.,* that peptides that are immunogenic can be used at high doses to induce tolerance. In addition, the WO 94/06828 document cited in the instant specification (on page 30 at lines 15-18) that is relied upon for disclosure that the peptide may be administered in high doses to produce high dose tolerance teaches substituted tolerizing peptides, *i.e.,* peptides that are generated by replacing each amino acid of the immunogenic peptide with a different amino acid residue and testing for tolerized T cells, *i.e.,* ones that will not proliferate when stimulated with low antigen concentrations.

The art recognizes that in order to be used for generating an immunogenic or tolerogenic response that said peptide must bind MHC and also present an epitope recognized by T cells. The art recognizes that the T cell epitope differs from the amino acids pertinent to MHC binding.

Evidentiary reference Karin *et al* (J. Exp. Med. 1994, 180: 2227-2237, of record) teaches that a single substitution in an amino acid residue, wherein said amino acid residue plays no role in MHC binding, can completely abrogate the immunogenicity of an otherwise immunogenic peptide (especially summary and Table 1). Thus Karen *et al* establish that amino acid residues not recited in the claimed "human" or "human pathogen" polypeptides, *i.e.,* TCR contact residues, will play a pivotal role in determining whether the peptides recited in the claims are capable of being immunogenic, and by extension tolerogenic.

Evidentiary reference Tisch and McDevitt (PNAS USA 1994, 91: 437-438, of record) teach that the high degree of specificity required for the process of clonal deletion/anergy may be limiting when dealing with diseases such as MS in which there are responses to several autoantigens and the critical inciting autoantigen(s) is not known (page 437, column 3 at the third full paragraph). Tisch and McDevitt teach that only in EAE, where defined antigens (MBP or Ac1-11 MBP peptide) have been used to induce disease, has antigen-specific immunotherapy clearly succeeded in treating an ongoing autoimmune response, and that the critical tests of systemic antigen-specific immunotherapy have yet to be done (page 438, column 1 at lines 6-12).

Evidentiary reference Anderton (Immunology 104: 367-376, 2001, of record) teaches that *in vivo* use of altered peptide ligands is unpredictable and dangerous in outbred human populations (especially paragraph spanning columns 1 and 2 on page 370). Evidentiary reference Chen *et al* (J. Immunol. 157: 3783-3790, 1996, of record) teach that analogue peptides with single amino acid residue substitutions that bind to HLA-DR4 were unpredictable in that some exhibit agonist activity, others exhibit antagonist activity, and still others exhibit antagonist activity with partial activation. Chen *et al* further teach that activation mediated by TCR recognition of the ligand is not an on/off event, and it may be quantitatively or qualitatively different depending on affinity and avidity between TCRs and their ligands.

Evidentiary reference Schwartz and Kipnis (The Neuroscientist 2002, 8(5): 405-413) teach that immunosuppression as a therapeutic strategy for CNS dysfunction should be weighed with extreme caution (last sentence of article). Schwartz and Kipnis teach that in patients with MS and other neurodegenerative diseases, where the aim is to block the autoimmune disorder while deriving the potential benefit of the autoimmune response, the effect of treatment should be immunomodulatory rather than immunosuppressive (abstract and the paragraph spanning pages 411 and 412).

The specification does not disclose the amino acid residues that constitute the T cell epitope in the peptide recited in the claim, with the exception of the specific peptides identified by amino acid sequence in the specification such as SEQ ID NO: 1-7 from the contiguous sequence of the PV autoantigen protein desmoglein 3, or such as SEQ ID NO: 8-15 from pathogen associated proteins. There is no disclosure of any "human pathogen polypeptide" that is associated with PV, nor of any "isolated human polypeptide" or protein comprising a subsequence that is an" isolated human polypeptide" other than those that derive from desmoglein-3 for PV.

Evidentiary reference Sercarz (Nature Biotechnology 21(9): 1017-1019, 2003, of record) teaches that to date, not one autoimmune disease has been successfully treated using a specific vaccine, and that typically, in those autoimmune diseases driven by proinflammatory T cell activity (*e.g.* MS), a plethora of antigens appear to be involved, making it difficult to attempt to devise a single specific tolerogenic vaccine. Sercarz further teaches that because appropriate experimental tolerance-inducing regimens have often failed to be chosen, the potential of a vaccine containing numerous antigens to exacerbate (rather than ameliorate) an autoimmune condition has been an understandable concern.

There is no guidance in the specification as to what alterations result in a functional polypeptide, *i.e.,* one that binds to a subtype of the recited HLA-DR *and* to a TCR *and* is capable of producing immunity or tolerization *in vivo*. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions/additions would be acceptable to retain functional activity, *i.e.,* bind to any number of undisclosed HLA-DR molecules, bind to a T cell and cause tolerization, it would require undue experimentation for one of skill in the art to arrive at amino acid sequences that would have functional activity. In other words, since it would require undue experimentation to identify amino acid sequences that have functional activity, it would require undue experimentation to make and/or use the corresponding sequences. The enablement provided by the specification is not commensurate with the scope of the claims.

Applicant's arguments in the amendment filed 8/31/05 have been fully considered but are not persuasive.

Applicant's position in the said amendment beginning on page 13 and continuing through page 16 is of record in Applicant's said amendment.

It is the Examiner's position with respect to Applicant's argument that four out of seven putative polypeptides meeting the structural requirements of new claim 32 that are recognized by T cells from PV patients (SEQ ID NO: 3 and 4 as disclosed in the instant specification and two others as disclosed in Wucherpfennig *et al.* PNAS USA 12/1995, 92: 11935-11939), is indicative that claim 32 is fully enabled, that Applicant has not demonstrated that such peptides are useful in producing any useful clinical endpoint, *i.e.,* that they are capable of tolerizing against an autoantigen and that that produces a useful result *in vivo*. In addition, the instant claims are not limited to polypeptides consisting of one of SEQ ID NO: 1-7, but rather are open to any polypeptide having either anchor residues for binding one of the subtypes of the recited HLA class II molecules, or having anchor residues and 3-4 TCR contact residues, the polypeptides either being from any number of proteins from humans or pathogens or not being a subsequence of said proteins, or being variants of either. The SEQ ID NO: 8-15, as well as the motifs SEQ ID NO: 18-20, were designed based upon the reactivity of small subgroups of T cell clones to one MBP peptide, so the "high success rate" asserted by Applicant as an indication that undue experimentation is not required, may not carry through for other polypeptides that are required to tolerize against other autoantigens, and including wherein those autoantigens are not known.

It is the Examiner's position with regard to Applicant's arguments to the number of peptides that must be screened not being more than 40 based upon the length and sequence of desmoglein-3, that the instant claims are not limited to a polypeptide that is a subsequence of desmoglein-3. It is the Examiner's position that the number of potential polypeptides is very large due to the number of proteins in an undisclosed number of pathogens (Applicant estimates this as no more than 100 proteins/viral genome), *i.e.,* for example, 100 proteins x 100 pathogens = 100,000 proteins, and 100,000 proteins contain an undisclosed number of subsequences possessing a motif for binding to a subtype of HLA-DR2 or HLA-DR4 associated with PV or MS. If just 10 peptide subsequences exist per protein, that is 1 million peptides. Applicant estimates less than 50,000 human proteins exist. This would constitute several million subsequences that would potentially possess the binding motif. If the polypeptides possessing the motif are not subsequences of proteins, then the number of potential polypeptides that could possess the motif is potentially unlimited, as the TCR contact amino acid residues are not specified. By fixing the P1, P4 and P6 positions according to the relevant motif, the skilled artisan would have to make 20^7 different peptides (*i.e.,* 1,280,000,000 or about 1 billion peptides) and screen them not only for binding to the relevant HLA-DR molecule(s), but also determine which are immunogenic and/or tolerogenic. In addition, evidentiary reference Reche *et al* teach that conserved regions flanking the core CD4 T cell epitopes (*i.e.,* class II binding epitopes) may contribute to immunogenicity, adding to the number of peptides.

It is the Examiner's position with regard to Applicant's argument that there is only one PV-associated HLA-DR4 subtype and one MS-associated HLA-DR2 subtype at the time of filing, the instant claims are not limited to the recitation of "HLA-DRβ1*0402" (for PV) or "HLA-DRβ1*1501" for MS.

It is the Examiner's position that knowledge of the pocket amino acid residues alone is not sufficient for determination of a binding motif as enunciated in the instant rejection.

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 32-35, 36, 41 and 42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3 and 4 of U.S. Patent No. 5,874,531. Although the conflicting claims are not identical, they are not patentably distinct from each other because the composition comprising the peptides of claims 3 and 4 of the '531 patent are encompassed by the instant claims.

The Examiner notes Applicant's remarks on page 17 in Applicant's amendment filed 8/31/05, *i.e.,* that Applicant will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 32 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohashi *et al* (Dev. Neuroscience 17(3): 189, July 8-10, 1995, Abstract) in view of De Bruijin *et al* (Eur. J. Immunol. 1991, 27: 2963-2970).

Ohashi *et al* teach hydrophilic polypeptide PLP 95-116 is an HLA-DR2 (HLA-DRβ1*1501) associated T cell epitope in MS, and that PBMC were stimulated *in vitro* with the said peptide, but do not teach the carrier the said polypeptide is dissolved in.

Ohashi *et al* do not teach the peptide in a pharmaceutical preparation, *i.e.,* formulated in a pharmaceutically acceptable carrier, such as PBS or IMDM.

De Bruijin *et al* teach that peptides corresponding to T cell epitopes were dissolved in PBS or serum-free Iscove's modified Dulbecco's medium (IMDM) for use in *in vitro* assays with T cells.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have formulated the peptide taught by Ohashi *et al* in the PBS or IMDM taught by De Bruijin *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to dissolve the peptide in a carrier that is compatible with the T cell assay taught by Ohashi *et al* in a like manner as was taught by De Bruijin *et al.*

Claims 32 and 38 are included in this rejection because it is an expected property of PBS that it is compatible with *in vivo* administration, and because it is an expected property of PBS or of IMDM that they are compatible with *in vivo* administration to a mouse.

9. Claims 32 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kondo and Ohashi (Nippon Rinsho. Japanese Journal of Clinical Medicine. 52(11): 2940-2945, 11/1994, Abstract) in view of De Bruijin *et al* (Eur. J. Immunol. 1991, 27: 2963-2970).

Kondo and Ohashi teach polypeptide PLP 95-116 is an HLA-DR2 (HLA-DRβ1*1501) associated T cell epitope in MS that was determined to be a T cell epitope by analysis with PLP-specific T cells.

Kondo and Ohashi do not teach the peptide in a pharmaceutical preparation, *i.e.,* formulated in a pharmaceutically acceptable carrier.

De Bruijin *et al* teach that peptides corresponding to T cell epitopes were dissolved in PBS or serum-free Iscove's modified Dulbecco's medium (IMDM) for use in *in vitro* assays with T cells, but do not teach the carrier the said polypeptide is dissolved in.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have formulated the peptide taught by Kondo and Ohashi *et al* in the PBS or IMDM taught by De Bruijin *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to dissolve the peptide in a carrier that is compatible with the T cell assay taught by Kondo and Ohashi *et al* in a like manner as was taught by De Bruijin *et al*.

Claims 32 and 38 are included in this rejection because it is an expected property of PBS that it is compatible with *in vivo* administration, and because it is an expected property of PBS or of IMDM that they are compatible with *in vivo* administration to a mouse.

10. Claims 32 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohashi *et al* (J. Neuroimmunology. 54(1-2): 186, Abstract) in view of De Bruijin *et al* (Eur. J. Immunol. 1991, 27: 2963-2970).

Ohashi *et al* teach polypeptide PLP 95-116 is an HLA-DR2 (HLA-DRβ1*1501) associated T cell epitope in MS, and teach that T cell lines were generated using the said peptide, but do not teach what the peptide was formulated in.

Ohashi *et al* do not teach the peptide in a pharmaceutical preparation, *i.e.,* formulated in a pharmaceutically acceptable carrier.

De Bruijin *et al* teach that peptides corresponding to T cell epitopes were dissolved in PBS or serum-free Iscove's modified Dulbecco's medium (IMDM) for use in *in vitro* assays with T cells.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have formulated the peptide taught by Ohashi *et al* in the PBS or IMDM taught by De Bruijin *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to dissolve the peptide in a carrier that is compatible with the T cell assay taught by Ohashi *et al* in a like manner as was taught by De Bruijin *et al*.

Claims 32 and 38 are included in this rejection because it is an expected property of PBS that it is compatible with *in vivo* administration, and because it is an expected property of PBS or of IMDM that they are compatible with *in vivo* administration to a mouse.

11. No claim is allowed.

12. It is noted by the Examiner that Applicant's IDS filed 6/11/98 is missing the Form-1449.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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November 25, 2005

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